IR ($CHCl_3$) 3546, 1466, 1334, 1243, 1031 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (d, 3, J = 7 Hz), 3.40 (br d, 2, J = 6 Hz), 2.90–3.53 (m, 1), 3.85 (s, 3), 4.83–5.30 (m, 2), 5.01 (d, 1, J = 9 Hz), 5.68 (s, 1), 5.95 (s, 2), 5.47–6.40 (m, 1), 6.53 (br s, 1), 6.72–7.00 (m, 3); MS m/e (relative intensity, %) 340 (M^+, 100).

7-Allyl-6-hydroxy-5-methoxy-3-methyl-2-(3,4-methylenedioxyphenyl)benzofuran (11). Starting with 107 mg (0.3 mmol) of **18**, 98 mg of crude dihydrobenzofuran **9** was obtained using the conditions described above. The crude dihydrobenzofuran **9** was then dissolved in THF (1 mL) and cooled in an ice bath while a solution of DDQ (65 mg, 0.3 mmol) in THF (1 mL) was added dropwise to it. After 10 min, the contents were diluted with ether and then washed with water. The aqueous washing was back extracted with ether, and the combined ether extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using hexane–EtOAc (6:1 v/v) as solvent to give 45 mg (42%) of **11**: mp 123–124 °C (hexane–diethyl ether); IR ($CHCl_3$) 3567, 1475, 1350, 1258, 1046 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3), 3.72 (br d, 2, J = 7 Hz), 3.94 (s, 3), 4.98–5.33 (m, 2), 5.83 (s, 1), 6.01 (s, 2), 5.89–6.40 (m, 1), 6.80 (s, 1), 6.91 (d, 1, J = 8 Hz), 7.18–7.36 (m, 2); UV (95% EtOH) 254 nm(log ϵ 3.92), 290(sh, 4.16), 328 (4.51);[9] MS m/e (relative intensity, %) 338 (M^+, 100).

Acknowledgment. We are indebted to the National Institutes of Health (GM 09686) and the Hoffmann-La Roche Foundation for financial support. High-resolution mass spectra were measured in the National Institutes of Health supported facility at the Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.

Registry No.—**2,** 4043-71-4; **9,** 67010-45-1; **10,** 66967-24-6; **11,** 57467-91-1; **12,** 66967-25-7; **14,** 66967-26-8; **15,** 66967-27-9; **18,** 66967-28-0; allyl bromide, 106-95-6.

References and Notes

(1) G. Büchi and C.-P. Mak, *J. Am. Chem. Soc.*, **99,** 8073 (1977).
(2) M. V. vonBülow, N. C. Franca, O. R. Gottlieb, and A. M. P. Suarez, *Phytochemistry,* **12,** 1805 (1973).
(3) O. A. Lima, O. R. Gottlieb, and M. Taveira Magalhaes, *Phytochemistry,* **11,** 2031 (1972); O. R. Gottlieb, J. C. Mourao, M. Yoshida, Y. P. Mascarenhas, M. Rodrigues, R. D. Rosenstein, and K. Tomita, *ibid.*, **16,** 1003 (1977).
(4) O. R. Gottlieb, M. Leao DaSilva, and Z. S. Ferreira, *Phytochemistry,* **14,** 1825 (1975). Professor O. R. Gottlieb has kindly confirmed the identities of natural and synthetic **9** and **11** by direct comparison.
(5) A. Ogiso, M., Kurabayashi, S. Takahashi, H. Mishima, and M. C. Woods, *Chem. Pharm. Bull.*, **18,** 105 (1970).
(6) C. J. Aiba, J. B. Fernandes, O. R. Gottlieb, and J. G. Soares Maia, *Phytochemistry,* **14,** 1597 (1975).
(7) This phenol was prepared previously from 3,4-dimethoxybenzaldehyde in nine steps: R. T. Arnold and F. Bordwell, *J. Am. Chem. Soc.*, **64,** 2983 (1942); R. T. Arnold and N. Bortnick, *ibid.*, **67,** 806 (1945).
(8) G. Büchi, P.-S. Chu, A. Hoppmann, C.-P. Mak, and A. Pearce, *J. Org. Chem.*, submitted for publication.
(9) The values given in ref 4 are 250, 290, and 337 nm (log ϵ 3.83, 4.06, and 4.44).

A Useful Synthesis of 3-Oxodihydroisoindoles

P. S. Anderson,* M. E. Christy, C. D. Colton, and K. L. Shepard

Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

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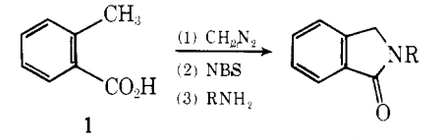
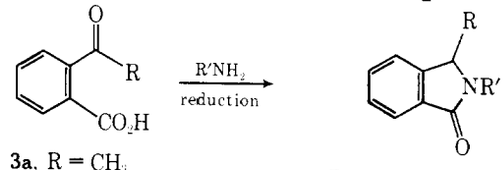
A useful one-step conversion of *o*-acylbenzoic acids (**3**) to 3-oxodihydroisoindoles (**4**) has been developed. Thus, reductive amination of **3** with a primary amine, the amine hydrochloride, and sodium cyanoborohydride or sodium borohydride in acetonitrile effected the conversion of **3** to **4**. The success of this method is dependent on the initial formation in acetonitrile of a 1-alkyl-1-(alkylamino)dihydroisobenzofuran-3-one, a "ring tautomer" such as **7**, which on protonation is reduced rapidly to **4** by these metal hydrides. Other nucleophiles (CH_3NH_2 and CN^-) were substituted for the metal hydrides to synthesize 1-substituted analogues of **4** such as 1,2-dimethyl-1-cyano-3-oxodihydroisoindole (**6**).

In the preparation of isoindoles[1] as well as the elaboration of certain natural products,[2,3] 3-oxodihydroisoindoles have served as important synthetic intermediates. Routes of limited utility to these lactams have been described.[4,5] In addition, Danishefsky has reported a useful two-step method to convert methyl *o*-toluate to *N*-methyl-3-oxodihydroisoindole (eq 1).[2] What we believe to be an equally attractive route to 3-oxodihydroisoindoles in general and a better route from *o*-acylbenzoic acids to 1,2-disubstituted analogues specifically is set forth below (eq 2).



1 2 (1)



(2)

3a, R = CH_3
b, R = C_2H_5
c, R = n-C_3H_7
d, R = H
e, R = C_6H_5

4a, R = R′ = CH_3
b, R = CH_3; R′ = C_2H_5
c, R = CH_3; R′ = n-C_3H_7
d, R = CH_3; R′ = 
e, R = CH_3; R′ = $C_6H_5CH_2$
f, R = C_2H_5; R′ = CH_3
g, R = n-C_3H_7; R′ = CH_3
h, R = H; R′ = CH_3
i, R = CH_3; R′ = $CH(CH_3)_2$

These lactams (**4**) were required as intermediates for the synthesis of 1,2,3-trisubstituted isoindoles, a class of compounds which has received very limited attention in the literature.[6] Initially, commercially available *o*-acetylbenzoic acid (**3a**) was hydrogenated to *o*-ethylbenzoic acid, and this acid was carried through the three-step process of eq 1 with methylamine as the base to provide **4a.** Although this approach was successful with several other primary amines, it was apparent that an alternate direct route (eq 2) from *o*-acylbenzoic acids **3** to the desired lactams **4** offered certain advantages. Thus, the acids **3** are more readily available either commercially[7] or by synthesis[8] than the corresponding *o*-alkylbenzoic acids which, in fact, frequently are prepared from **3.** Furthermore, this synthesis in comparison with that of eq 1 involved fewer operational steps and avoided the handling of the intermediate bromo esters which are potent lachrymators.

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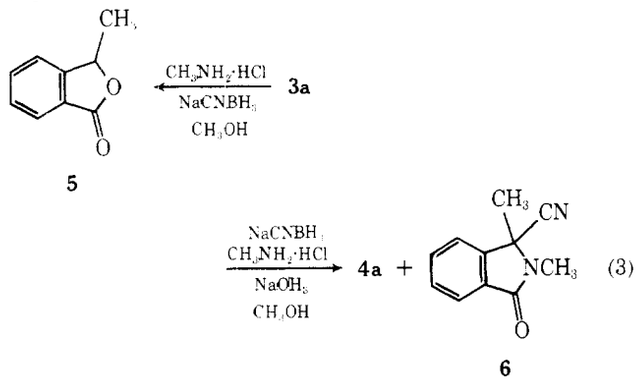
Table I. ^{13}C NMR Chemical Shifts[a] (ppm) in $CDCl_3$

Assignment	Compound no. 5	3a	7	7 HCl	4a	12	13	13 HCl
C-CH_3	20.4	26.7	27.0	25.1	17.9	23.0	22.8	21.8
N-CH_3 (exo)			28.8	32.3			28.3	25.0[b]
N-CH_3 (ring)					26.9	23.4	25.2	25.6[b]
Benzylic	77.7	*d*	107	*d*	57.6	88.3	78.8	78.2
Aromatic	121.7	122.7	122.5	125.1	121.8	121.6	121.7	123.3
Aromatic	125.6	126.3	125.6	127.5	123.4	122.9	123.2	124.0
Aromatic	125.8	126.3	128.4	129.8	128.0	129.1	128.8	131.2
Aromatic	129.1	130.4	130.0	131.7	132.0	130.2	132.0	131.4
Aromatic	134.1	134.5	134.0	134.4	133.3	132.1	132.5	133.6
Aromatic	151.3[c]	148.9	148.6	137.3	146.8	148.4	147.4	140.6
Carbonyl	170.4	168.9	169.2	166.5	168.0	166.9	167.2	167.3

[a] Relative to internal $(CH_3)_4Si$. [b] These assignments may be reversed. [c] Chemical shifts in this row are for the aromatic carbon adjacent to the benzylic carbon of the "ring tautomers". [d] This carbon atom was not observed due to broadening caused by interconversion of "ring and chain tautomers".

Reductive amination with a primary amine and sodium cyanoborohydride[9] ($NaCNBH_3$), a reagent with high selectivity for carbon–nitrogen double bonds, was assumed to be the ideal method for a one-step conversion of **3** to **4** since the concentration of intermediate imine would be expected to be low with an aromatic ketone. In practice, however, addition of $NaCNBH_3$ to a methanol solution of *o*-acetylbenzoic acid (**3a**) and methylamine hydrochloride gave only the lactone **5** (eq 3). The desired lactam **4a** was obtained on treatment of



3a or the sodium salt of **3a** with methylamine, methylamine hydrochloride, and $NaCNBH_3$; however, it was contaminated with 15–20% of a byproduct **6**.

The probability that cyanide (derived hydrolytically from the $NaCNBH_3$ in this reaction medium) was adding to the imine intermediate to form **6** prompted a solvent change to acetonitrile. Thus, a solution of **3a** in acetonitrile was treated with anhydrous methylamine followed by addition of methylamine hydrochloride and $NaCNBH_3$. These conditions effected the conversion of **3a** to **4a** in high yield with no detectable contamination by either **5** or **6**. Surprisingly, substitution of sodium borohydride ($NaBH_4$) for $NaCNBH_3$ gave the same result in this case.

The generality of this method was tested using **3a** with $NaCNBH_3$ and the following primary amines: ethyl-, *n*-propyl-, 2-propyl-, cyclopropyl-, benzyl-, and *tert*-butylamines. High yield conversions to the corresponding lactams **4** were observed except with 2-propyl-[10] and *tert*-butylamines. In these cases, the only product isolated was the lactone **5**. This method was further tested using methylamine and either $NaBH_4$ or $NaCNBH_3$ with the following *o*-acylbenzoic acids: *o*-propionyl- (**3b**), *o*-butyryl- (**3c**), *o*-formyl- (**3d**), and *o*-benzoylbenzoic acids (**3e**). Good yields of the lactams were obtained with the exception of **3e**, which gave only a lactone product.

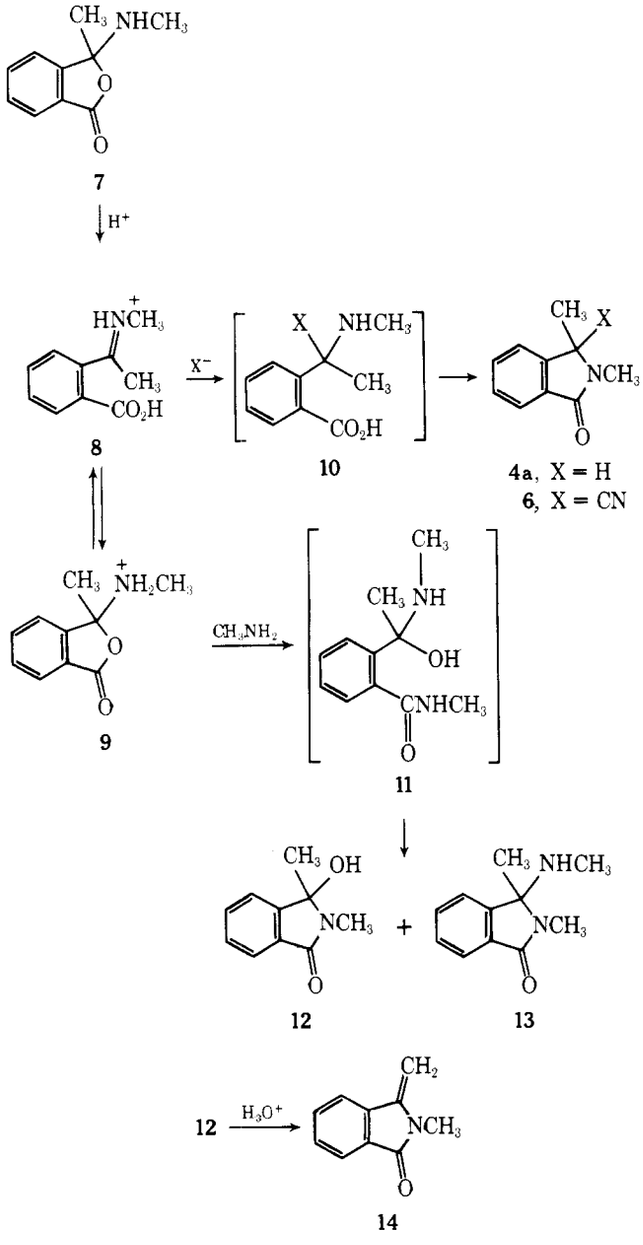
In order to examine this reaction in more detail, a solution of **3a** in acetonitrile was saturated with anhydrous methylamine and then evaporated. The resulting crystalline white solid exhibited spectral properties (see Experimental Section and Table I) totally consistent with the ring tautomer **7**. The ^1H NMR chemical shifts for the C-CH_3 and N-CH_3 groups of **7** remain constant in Me_2SO-d_6, $CDCl_3$, and CD_3CN, while the NMR spectra of systems such as **3a**, which may exist as ring and chain tautomers, are solvent dependent.[11] When the reaction of **3a** with methylamine was monitored by ^1H NMR spectroscopy, the conversion of **3a** to **7** was so rapid that the intermediate carbinolamine and imine were not observed.

The ring tautomer **7** was hydrolyzed readily to **3a** on exposure to dilute aqueous acid. Solutions of **7** in aprotic solvents, however, were remarkably stable. Thus, recrystallization of **7** from hot hexane could be carried out with minimal loss, and **7** could be recovered from acetonitrile solution to which either methylamine, methylamine hydrochloride, or $NaCNBH_3$ had been added. The conversion of **7** to **4a** occurred only when the latter two reagents (methylamine hydrochloride and $NaCNBH_3$) were both present in the reaction medium. However, **7** underwent reduction to a mixture of products including **5** and **4a** when $NaBH_4$ alone was added. Again, the combination of $NaBH_4$ and methylamine hydrochloride was required for smooth conversion of **7** to **4a** in acetonitrile.

These results suggested that protonation of **7** was instrumental in the reduction process. Thus, addition of methylamine hydrochloride could effect conversion of **7** to the protonated ring chain tautomers **8** and **9**, which should exhibit enhanced reactivity toward metal hydride reducing agents and other added nucleophiles. To test this concept, sodium cyanide (NaCN) was added to an acetonitrile solution of **7**. After 3 h, conversion of **7** to the cyanide adduct **6** could not be detected (TLC). The subsequent addition of methylamine hydrochloride to this solution, however, resulted in the rapid efficient conversion of **7** to **6**. That the amine hydrochloride was serving solely as a proton source was supported by the observation that substitution of ethylamine hydrochloride for methylamine hydrochloride did not change the product composition in either this reaction or the hydride reduction of **7** to **4a**. Furthermore, while **7** was recovered after standing for 24 h in acetonitrile containing methylamine, the addition of methylamine hydrochloride to this solution slowly (24 h) transformed **7** to a mixture of **12** and **13**. These results are illustrated in Scheme I.

That **12** and **13** have the ring tautomer structure was clearly evident both from their ^{13}C NMR spectra and from the fact that they could be recovered from acetonitrile solution after treatment with $NaBH_4$ and methylamine hydrochloride. The lactam **13** also was stable in aqueous hydrochloric acid and could be isolated as a hydrochloride. The lactam **12** on similar

Scheme I



treatment gave the unstable dehydration product **14.**

Thus, **7** on protonation is transformed to the ring and chain tautomers **8** and **9,** which are converted to products by added nucleophiles. Although this process was not observable directly by ^1H NMR spectroscopy due to the low concentration (~1%) of **8** and **9** under the reaction conditions, a comparison of the ^{13}C NMR spectra (Table I) of **7** and **7** HCl supported this concept. Thus, the resonance (107 ppm) for the benzylic carbon atom in **7** disappears in the spectrum of **7** HCl due to line broadening as a consequence of the equilibrium **8** ⇄ **9.** The benzylic carbon atom also is not observed in **3a,** which is a mixture of ring and chain tautomers. Furthermore, the chemical shift for the comparable carbon atom in **13** is not changed appreciably by protonation of the nitrogen consistent with the view that both species are ring tautomers. In addition, the aromatic ring carbon adjacent to this center exhibits a much larger (11.3 ppm) upfield shift on protonation of the nitrogen in **7** than is observed for protonation of **13** (6.8 ppm).[12] Lastly, the product compositions outlined in Scheme I are best understood in terms of the equilibrium **8** ⇄ **9.**

In conclusion, a useful one-step method for converting *o*-acylbenzoic acids to 1,2-disubstituted 3-oxodihydroisoindoles has been described. This transformation passes through a 1-alkyl-1-(alkylamino)isobenzofuran-3-one intermediate which is subsequently protonated and reduced by metal hydrides. The only limitations to this method are its failure with highly hindered amines (*tert*-butylamine) and aromatic ketones (*o*-benzoylbenzoic acid).

Experimental Section

Melting points (Thomas-Hoover melting point apparatus) and boiling points are uncorrected. Spectra were obtained as follows: IR spectra on a Perkin-Elmer 237; mass spectra on an AEI MS 902 by direct insertion; ^1H NMR spectra on a Varian T-60 or EM 390 spectrometer using $(CH_3)_4Si$ as an internal standard; and ^{13}C NMR spectra on a Varian CFT-20. GLC was performed on a Hewlett-Packard Model 5700A/3370B GLC using a glass column (6 ft × 2 mm) packed with 1% OV-17 on 100 *N* 120 mesh Gas-Chrom Q with a helium flow rate of 32 mL/min.

1,2-Dimethyl-3-oxodihydroisoindole (4a). To a solution of methylamine (1.8 g, 0.06 mol) in acetonitrile (150 mL) was added **3a** (4.1 g, 0.025 mol) followed after 15 min by methylamine hydrochloride (3.4 g, 0.05 mol) and $NaCNBH_3$ (2.0 g, 0.03 mol). The reaction mixture was stirred for 3 h. The solvent was removed under reduced pressure and the residue slurried with H_2O. The pH was adjusted to 4 with concentrated HCl, and the resulting solution was extracted with chloroform (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. Distillation of the concentrate gave 3.5 g (87%) of **4a:** bp 95–97 °C (0.3 Torr); ^1H NMR ($CDCl_3$) δ 1.5 (d, 3 H, CCH_3, J = 7 Hz), 3.1 (s, 3 H, NCH_3), 4.4 (q, 1 H, benzylic, J = 7 Hz), 7.4–7.9 (m, 4 H, aromatic); IR (neat) 1685 (C=O) cm^{-1}; MS *m/e* (%) 161 (33, M^+), 146 (100, $M^+ - CH_3$); GLC (99%), retention time 2.8 min (130 °C).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.53; H, 6.83; N, 8.69. Found: C, 74.91; H, 6.95; N, 8.41.

1-Methyl-2-ethyl-3-oxodihydroisoindole (4b). Compound **4b** was prepared from **3a** (3.3 g, 0.02 mol), ethylamine (4.5 g, 0.1 mol), ethylamine hydrochloride (4.05 g, 0.05 mol), and $NaCNBH_3$ (2.0 g, 0.03 mol) in acetonitrile (150 mL) as described for the synthesis of **4a.** Distillation gave 2.8 g (86%) of **4b:** bp 98–102 °C (0.1 Torr); ^1H NMR ($CDCl_3$) δ 1.0 (t, 3 H, NCH_2CH_3, J = 7 Hz), 1.2 (d, 3 H, CCH_3, J = 7 Hz), 3.3 (m, 1 H, NCH_2), 3.7 (m, 1 H, NCH_2), 4.8 (q, 1 H, benzylic, J = 7 Hz), 7.4–8.0 (m, 4 H, aromatic); IR (neat) 1690 (C=O) cm^{-1}; MS *m/e* (%) 177 (11, M^+), 162 (100, $M^+ - CH_3$); GLC (99%), retention time 7.5 min (130 °C).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.15; H, 7.09; N, 7.91.

1-Methyl-2-*n*-propyl-3-oxodihydroisoindole (4c). Compound **4c** was prepared from **3a** (3.3 g, 0.02 mol), *n*-propylamine (5.9 g, 0.1 mol), *n*-propylamine hydrochloride (4.8 g, 0.05 mol), and $NaCNBH_3$ (2.0 g, 0.03 mol) as described for **4a.** Distillation gave 3.3 g (88%) of **4c:** bp 98–102 °C (0.1 Torr); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, $N(CH_2)_2CH_3$, J = 7 Hz), 1.4 (d, 3 H, CCH_3, J = 7 Hz), 1.6–2.0 (m, 2 H, NCH_2CH_2), 3.2 (m, 1 H, NCH_2), 3.9 (m, 1 H, NCH_2), 4.5 (q, 1 H, benzylic, J = 7 Hz), 7.4–8.0 (m, 4 H, aromatic); IR (neat) 1690 (C=O), cm^{-1}; MS *m/e* (%) 189 (6, M^+), 174 (100, $M^+ - CH_3$), 160 (30, $M^+ - C_3H_7$); GLC (99.3%), retention time 7.7 min (130 °C).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.93; N, 7.40. Found: C, 75.90; H, 8.19; N, 7.12.

1-Methyl-2-cyclopropyl-3-oxodihydroisoindole (4d). A solution of **3a** (3.3 g, 0.02 mol) and cyclopropylamine (5.7 g, 0.1 mol) was stirred overnight. To this solution was added cyclopropylamine hydrochloride (4.7 g, 0.05 mol) followed by the portionwise addition (six equal portions over 60 min) of $NaBH_4$ (1.2 g, 0.03 mol). The solvent was removed under reduced pressure, the residue slurried with H_2O (75 mL), the pH adjusted to 4 with concentrated HCl, and the resulting solution extracted with chloroform (4 × 75 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Distillation of the concentrate gave 3.0 g (80%) of **4d:** bp 131–133 °C (0.1 Torr); ^1H NMR ($CDCl_3$) δ 0.6–1.2 (m, 4 H, methylene), 1.6 (d, 3 H, CH_3, J = 7 Hz), 2.7 (m, 1 H, NCH), 4.5 (q, 1 H, benzylic, J = 7 Hz), 7.2–8.0 (m, 4 H, aromatic); IR (neat) 1675 (C=O) cm^{-1}; MS *m/e* (%) 187 (77, M^+), 172 (100, $M^+ - CH_3$); GLC (92%), retention time 6.0 min (130 °C). An analytical sample was obtained from a center cut of the distillate.

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.49. Found: C, 77.41; H, 6.91; N, 7.30.

1-Methyl-2-benzyl-3-oxodihydroisoindole (4e). Compound **4e** was prepared from **3a** (32.8 g, 0.2 mol), benzylamine (64.3 g, 0.6 mol), benzylamine hydrochloride (57 g, 0.4 mol), and $NaBH_4$ (5.3 g, 0.14

mol) in acetonitrile (1000 mL) as described for **4d.** Distillation gave 29 g (61%) of **4e:** bp 158–162 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.4 (d, 3 H, CCH_3, J = 7 Hz), 4.2 (d, 1 H, $C_6H_5CH_2$, J = 15 Hz), 4.3 (q, 1 H, benzylic, J = 7 Hz), 5.3 (d, 1 H, $C_6H_5CH_2$, J = 15 Hz), 7.2–8.0 (m, 4 H, aromatic); IR (neat) 1670 (C=O) cm^{-1}; MS m/e 237 (M^+), 222 ($M^+ - CH_3$), 147 ($M^+ - C_7H_7$) GLC (98.8%), retention time 10.6 min (160 °C).

Anal. Calcd for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.90. Found: C, 80.71; H, 6.17; N, 6.11.

1-Ethyl-2-methyl-3-oxodihydroisoindole (4f). Compound **4f** was synthesized from **3b** (3.5 g, 0.02 mol), methylamine (3.1 g, 0.1 mol), methylamine hydrochloride (6.75 g, 0.1 mol), and $NaCNBH_3$ (2.0 g, 0.03 mol) in acetonitrile as described for **4a.** Distillation gave 3.0 g (86%) of **4f:** bp 100–103 °C (0.3 Torr); ^{1}H NMR ($CDCl_3$) δ 0.6 (t, 3 H, CCH_3, J = 6 Hz), 2.0 (m, 2 H, CCH_2), 3.1 (s, 3 H, NCH_3), 4.5 (t, 1 H, CH, J = 4 Hz), 7.4–8.0 (m, 4 H, aromatic); IR (neat) 1690 (C=O) cm^{-1}; MS m/e (%) 175 (7, M^+), 146 (100, $M^+ - C_2H_5$); GLC (98.8%), retention time 4.9 min (130 °C).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.08; H, 7.19; N, 8.13.

1-Propyl-2-methyl-3-oxodihydroisoindole (4g). Compound **4g** was prepared from **3c** (3.8 g, 0.02 mol), methylamine (3.1 g, 0.1 mol), methylamine hydrochloride (6.75 g, 0.1 mol), and $NaBH_4$ (1.2 g, 0.03 mol) in acetonitrile (150 mL) as described for **4d.** Distillation gave 2.8 g (80%) of **4g:** bp 102–106 °C (0.4 Torr); ^{1}H NMR ($CDCl_3$) δ 0.8–2.0 (m, 7 H, $CH_2CH_2CH_3$), 3.0 (s, 3 H, NCH_3), 4.4 (t, 1 H, benzylic, J = 4 Hz), 7.2–7.9 (m, 4 H, aromatic); IR (neat) 1690 (C=O) cm^{-1}; MS m/e (%) 189 (5, M^+), 146 (100, $M^+ - C_3H_7$); GLC (96%), retention time 5.1 min (130 °C). A center cut of the distillate was used as an analytical sample.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.41. Found: C, 76.41; H, 8.11; N, 7.13.

2-Methyl-3-oxodihydroisoindole (4h). Compound **4h** was prepared from **3d** (3.0 g, 0.02 mol) as described for **4g.** Distillation gave 2.0 g of **4h,** bp 135–140 °C (2 Torr), which crystallized. Recrystallization from cyclohexane gave 1.4 g (46%) of **4h:** mp 116–118 °C (lit.[13] mp 116.5 °C); ^{1}H NMR ($CDCl_3$) δ 3.1 (s, 3 H, NCH_3), 4.2 (s, 2 H, NCH_2), 7.3–7.9 (m, 4 H, aromatic); IR (Nujol) 1675 (C=O) cm^{-1}.

Anal. Calcd for C_9H_9NO: C, 73.32; H, 6.11; N, 9.50. Found: C, 73.41; H, 5.94; N, 9.89.

1-Methyl-2-(2-propyl)-3-oxodihydroisoindole (4i). A solution of **3a** (3.3 g, 0.02 mol) and 2-propylamine (5.9 g, 0.1 mol) in acetonitrile (200 mL) was heated under reflux for 18 h. The solvent was evaporated and the residue extracted into hot hexane. Cooling gave 3.3 g of crystalline 1-methyl-1-(2-propylamino)isobenzofuran-3-one: mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 6 H, CCH_3, J = 6 Hz), 1.9 (s, 3 H, CCH_3), 2.8 (m, 2 H, CH and NH), 7.4–8.0 (m, 4 H, aromatic); IR (Nujol) 1740 cm^{-1}.

This compound was dissolved in acetonitrile (100 mL) to which was added anhydrous HCl (0.7 g) and $NaBH_4$ (0.76 g, 0.02 mol). After stirring overnight, the solvent was evaporated and the residue slurried with 0.1 M aqueous HCl. The pH was adjusted to 8 with concentrated aqueous NH_3 and the mixture extracted with chloroform (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Distillation of the concentrate gave 2.6 g (70%) of **4i:** bp 88–91 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.0 and 1.09 (dd, 6 H, $CH(CH_3)_2$, J = 6 Hz), 1.25 (d, 3 H, CCH_3, J = 6 Hz), 4.0 (p, 1 H, $CH(CH_3)_2$, J = 6 Hz), 4.25 (q, 1 H, benzylic, J = 6 Hz), 7–7.8 (m, 4 H, aromatic); IR (neat) 1685, 1230, 760, 720, 690 cm^{-1}; MS m/e (%) 189 (18, M^+), 174 (100, $M^+ - CH_3$), 132 (32), 131 (28), 103 (13).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.93; N, 7.40. Found: C, 76.11; H, 7.98; N, 7.31.

1-Methyl-1-(methylamino)isobenzofuran-3-one (7). Anhydrous methylamine (1.6 g, 0.05 mol) was introduced through a gas inlet tube into a solution of **3a** (1.64 g, 0.01 mol) in acetonitrile (100 mL). After stirring for 15 min, the solution was concentrated to dryness under reduced pressure and the residue was recrystallized from hexane to yield 1.5 g (85%) of **7:** mp 110–113 °C; ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 3 H, CCH_3), 2.2 (s, 3 H, NCH_3), 2.5 (s, 1 H, NH), 7.3–7.9 (m, 4 H, aromatic); MS m/e (%) 177 (6, M^+), 162 (77), 147 (100), 132 (78); IR (Nujol) 3340 (NH), 1740 (C=O), 1030, 860, 730, 710 cm^{-1}; pK_a(H_2O) = 8.5.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.84; H, 6.26; N, 8.06.

Conversion of 7 to 7 Hydrochloride. A solution of **7** in $CHCl_3$ was treated with anhydrous HCl and then filtered and concentrated to dryness under reduced pressure. Recrystallization of the residue from $CHCl_3$–hexane gave **7** hydrochloride: mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3 H) and 2.78 (s, 3 H) (CCH_3 and NCH_3), 7.4–8.2 (m, 6 H, aromatic and 2 H exchanged by D_2O); IR (Nujol) 2700, 2580, 2460, 1695 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.23; H, 5.66; N, 6.55. Found: C, 55.91; H, 5.72; N, 6.61.

Reaction of 7 with Methylamine Hydrochloride and NaCN. A solution of **3a** (2.5 g, 0.015 mol) and methylamine (2.3 g, 0.075 mol) in acetonitrile (100 mL) was slurried with methylamine hydrochloride (5.1 g, 0.075 mol) for 20 min and then treated with NaCN (1.8 g). After stirring for 18 h, the solvent was evaporated, water added, the pH adjusted to 3 with concentrated HCl, and the reaction mixture extracted with $HCCl_3$ (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated. Recrystallization of the solid residue from cyclohexane gave 2.0 g (71%) of **6,** mp 101–103 °C. The spectral properties of this sample were identical with those of the sample prepared below.

1,2-Dimethyl-3-oxodihydroisoindol-1-ol (12) and 1,2-Dimethyl-1-methylamino-3-oxodihydroisoindole (13). A solution of **3a** (3.28 g, 0.02 mol), anhydrous methylamine (3.1 g, 0.1 mol), and methylamine hydrochloride (1.35 g, 0.02 mol) in acetonitrile (300 mL) was stirred for 48 h and filtered, and the filtrate was evaporated under reduced pressure. The residue was extracted with chloroform (100 mL) and filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate containing 2% methanol as eluent. Eluted first was **12:** mp 127–129 °C (lit.[14] mp 128–130 °C); ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3 H, CCH_3), 2.65 (s, 3 H, NCH_3), 4.8 (br s, 1 H, OH), 7.2–7.6 (m, 4 H, aromatic); IR (Nujol) 3240, 1675 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.61; H, 6.36; N, 7.68.

Eluted second was **13:** mp 104–107 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3 H, CCH_3), 1.77 (s, 3 H, $NHCH_3$), 2.53 (s, 1 H, NH), 2.93 (s, 3 H, NCH_3), 7.3–7.8 (m, 4 H, aromatic); MS m/e (%) 190 (1, M^+), 175 (2, $M^+ - CH_3$), 160 (100, $M^+ - NHCH_3$); IR (Nujol) 3300, 1670 (C=O), 1170, 790, 700 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_2O$; C, 69.47; H, 7.36; N, 14.74. Found: C, 69.67; H, 7.66; N, 14.87.

Conversion of 13 to 13 Hydrochloride. A solution of **13** in chloroform was treated with anhydrous HCl and filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from hexane–chloroform to yield **13** hydrochloride: mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3 H) and 2.2 (s, 3 H) ($NHCH_3$ and CCH_3), 3.27 (s, 3 H, NCH_3), 7.3–8.2 (m, 5 H, aromatic and NH_2); IR (Nujol) 2660, 2520, 2500, 2480, 1715 (C=O), 1585, 1080,1110, 700, 770 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}ClN_2O$: C, 58.27; H, 6.67; N, 12.35. Found: C, 58.20; H, 6.56; N, 12.30.

Reaction of 3a with Methylamine Hydrochloride and $NaCNBH_3$ in Methanol. A solution of **3a** (16.4 g, 0.1 mol), methylamine hydrochloride (13.5 g, 0.2 mol), and $NaCNBH_3$ (6.5 g, 0.1 mol) in methanol (200 mL) was stirred for 24 h. The solvent was removed under reduced pressure, and the residue was slurried with 1.5 N aqueous HCl (300 mL) and extracted with chloroform (4 × 75 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was evaporated to yield 13.6 g (92%) of **5:** ^{1}H NMR ($CDCl_3$) δ 1.6 (d, 3 H, CCH_3, J = 7.5 Hz), 5.55 (q, 1 H, benzylic, J = 7.5 Hz), 7.2–7.9 (m, 4 H, aromatic); MS m/e 148 (M^+), 133 ($M^+ - CH_3$) 105 ($C_6H_5CO^+$); GLC 99%. These spectral properties were identical with those of **5** from independent synthesis.[5,15]

Reaction of 3a with Methylamine Hydrochloride, NaOH, and $NaCNBH_3$ in Methanol. To a solution of **3a** (24.6 g, 0.15 mol) in methanol (300 mL) was added NaOH (6 g, 0.15 mol) followed by methylamine hydrochloride (68 g, 1.0 mol) and $NaCNBH_3$ (9.75 g, 0.15 mol). After stirring for 24 h, the solvent was removed under reduced pressure and the residue slurried with 3 N aqueous HCl (500 mL). The pH was adjusted to 8.5 (aqueous NH_3) and the solution extracted with chloroform (4 × 100 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was evaporated to yield a liquid (28.9 g). GLC analysis indicated two components (**4a** and **6**) in a 70:30 ratio. Fractional distillation (0.25 Torr) separated 10 g of **4a** (bp 100–103 °C) and gave a fraction (10 g) containing a mixture of **4a** and **6.** The pot residue (5.35 g) crystallized and was recrystallized from cyclohexane to yield 3.7 g of **6:** mp 101–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 3 H, CCH_3), 3.2 (s, 3 H, NCH_3), 8.0 (m, 4 H, aromatic); MS m/e 186 (M^+); IR (KBr) 2200 (C≡N), 1690 (C=O) cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_2O$; C, 70.67; H, 5.78; N, 14.99. Found: C, 71.00 H, 5.55; N, 14.96.

Hydrolysis of 12. A solution of **12** (0.88 g, 0.005 mol) in 6 N aqueous HCl (20 mL) was warmed to 80 °C for 45 min, cooled, and extracted with chloroform (4 × 20 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. TLC (silica gel; benzene–dioxane–acetic acid, 25:5:1) demonstrated this to be a six component mixture containing **12, 3a,** and **14.** Column chromatography on silica gel eluting with ethyl ace-

tate gave 0.18 g of **14:** ^{1}H NMR ($CDCl_3$) δ 3.23 (s, 3 H, NCH_3), 4.81 (d, 1 H, vinyl, J = 3 Hz), 5.17 (d, 1 H, vinyl, J = 3 Hz), 7.4–7.9 (m, 4 H, aromatic); MS *m/e* 161 (M^+), 104, 78, 66; IR (neat) 1700 (C=O), 770, 700 cm^{-1}.

Hydrolysis of 7. A solution of **7** (1.77 g, 0.01 mol) in 0.1 N aqueous HCl (15 mL) on standing overnight deposited crystalline **3a** (1.5 g). A solution of **7** (0.88 g, 0.005 mol) in 6 N aqueous HCl (20 mL) was warmed to 80 °C, cooled, and extracted with chloroform (4 × 20 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The ^{1}H NMR and TLC characteristics of the concentrate (0.7 g) were qualitatively identical with those of the crude reaction mixture obtained on hydrolysis of **12:** Chromatography on silica gel eluting with ethyl acetate gave 0.15 g of **14.**

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Registry No.—**3a,** 577-56-0; **3b,** 2360-45-4; **3c,** 19666-03-6; **3d,** 119-67-5; **4a,** 58083-35-5; **4b,** 58083-36-6; **4c,** 58083-39-9; **4d,** 58083-37-7; **4e,** 1726-16-5; **4f,** 66967-33-7; **4g,** 66967-34-8; **4h,** 5342-91-6; **4i,** 66967-35-9; **5,** 3453-64-3; **6,** 66967-36-0; **7,** 66967-29-1; **7** HCl, 66967-30-4; **12,** 29879-71-8; **13,** 66967-31-5; **13** HCl, 66967-32-6; **14,** 32360-90-0; methylamine, 74-89-5; sodium cyanoborohydride, 25895-60-7; ethylamine, 75-04-7; *n*-propylamine, 107-10-8; cyclopropylamine, 765-30-0; benzylamine, 100-46-9; 2-propylamine, 75-31-0.

References and Notes

(1) J. D. White and M. E. Mann, *Adv. Heterocycl. Chem.*, **10,** 113 (1969).
(2) S. Danishefsky, T. A. Bryson, and J. Puthenpurayil, *J. Org. Chem.*, **40,** 796 (1975).
(3) E. Breyer and S. Zbaida, *Tetrahedron*, **31,** 499 (1975).
(4) T. Sugasawa, T. Toyoda, and K. Sasakura, *Chem. Pharm. Bull.*, **22,** 771 (1974).
(5) A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Lett.*, 1241 (1965).
(6) Merck and Co., U.S. Patent 4 064 139, 1977.
(7) A series of *o*-acylbenzoic acids are available from Frinton Laboratories, Vineland, N.J.
(8) P. R. Jones and P. J. Desio, *J. Org. Chem.*, **30,** 4293 (1965).
(9) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93,** 2897 (1971).
(10) A modification of this procedure was employed successfully for the conversion of **3a** to **4i.** This method, which did not work when *tert*-butylamine was substituted for 2-propylamine, is described in detail in the Experimental Section. In this case, the conversion of **3a** to 1-methyl-1-(2-propylamino)-isobenzofuran-3-one was slow at room temperature but could be achieved by heating the solution under reflux for 18 h. Protonation of this intermediate with 2-propylamine hydrochloride was unsuccessful. Thus, the use of anhydrous HCl as a proton source was required in order to effect the $NaBH_4$ reduction to **4i.** Attempts to reduce without added HCl gave a complex mixture of products.
(11) J. Finkelstein, T. Williams, V. Toome, and S. Traiman, *J. Org. Chem.*, **32,** 3229 (1967).
(12) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 197.
(13) T. Cohen, R. M. Moran, Jr., and G. Sowinski, *J. Org. Chem.*, **26,** 1 (1961).
(14) H. Müller and M. Seefelder, *Justus Liebigs Ann. Chem.*, **728,** 88 (1969).
(15) T. Sato, K. Tamura, K. Maruyama, O. Ogawa, and T. Imamura, *J. Chem. Soc., Perkin Trans. 1,* 779 (1976).

Fries Rearrangement of Trimethylhydroquinone Diacetate. A Novel Hydroquinone to Resorcinol Transformation

Noal Cohen,* Rocco J. Lopresti, and Thomas H. Williams

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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Fries rearrangement of trimethylhydroquinone diacetate (**1b**) ($AlCl_3$, 220 °C) leads to 1-(2,6-dihydroxy-3,4,5-trimethylphenyl)ethanone (**4**) and not the expected (and previously reported) 1-(2,5-dihydroxy-3,4,6-trimethylphenyl)ethanone (**2a**). Resorcinol **4** arises via secondary rearrangements of the normal products **2a** and **2b.** A mechanistic rationale is proposed.

While pursuing synthetic studies aimed at (2*R*,4′*R*,8′*R*)-α-tocopherol (vitamin E),[1] we recently required dihydroxytrimethylacetophenone **2a** as a starting material. A search of the literature revealed two apparent preparations of this substance; however, the reported melting points were not in agreement. In 1938, von Werder and Jung[2] described **2a** as a yellow solid, mp 152 °C, prepared by Fries rearrangement of trimethylhydroquinone diacetate (**1b**) using aluminum chloride at 220 °C. On the other hand, Manecke and Bourwieg, in 1962, claimed that treatment of trimethylhydroquinone (**1a**) with boron trifluoride–acetic acid complex at 100 °C produced the monoacetate **2b** which, upon saponification, yielded **2a** obtained as a yellow solid, mp 111 °C. We have reinvestigated these transformations and now wish to report that while the latter material is, in fact, **2a,** the dihydroxyacetophenone isolated from high temperature aluminum chloride treatment of **1b** is the resorcinol **4.**

Results

Repetition of the boron trifluoride–acetic acid treatment of **1a**[3] smoothly gave **2b** which, in turn, yielded the acetyl hydroquinone **2a,** mp 107–108 °C, after exposure to methanolic sodium hydroxide. The spectral properties of this acetophenone as well as the derived diacetate **3** were in accord with the proposed structural arrangement (see below and Experimental Section).

In contrast, treatment of **1b** with aluminum chloride at 220 °C[2] led to a mixture of products which, although complex, was amenable to analysis by GC and GC–MS. While the major component was, in fact, a dihydroxytrimethylacetophenone (mol wt 194), its retention time was clearly different from that of **2a,** of which substance only trace amounts were detectable. In addition, two chromones were produced whose structures were subsequently proven to be **5a** and **5b** as proposed originally by von Werder and Jung.[2]

On a preparative scale, these three components could be isolated in quite pure form by column chromatography. The dihydroxyacetophenone so obtained was recrystallized several times yielding a yellow solid, mp 136–145 °C, which despite the broad melting range appeared homogeneous on GC analysis. For reasons that are not apparent, we were unable to obtain a sharp melting point for this substance through further recrystallization; nonetheless, we assume it is identical with the product for which von Werder and Jung reported mp 152 °C.

The ^{1}H NMR spectrum of this acetophenone was revealing in its relative simplicity (four singlets in a ratio of 2:3:3:6) which, in contrast to that of **2a** (six singlets in a ratio of 1:1:

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